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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/586,156	06/02/00	ARNOLD L	IN-0016-1

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EXAMINER	
LU,F	
ART UNIT	**PAPER NUMBER**
1655	2

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/586,156	Arnold et al.,
Examiner	**Group Art Unit**
Frank Lu	1655

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Location of Application

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1655.

Drawings

2. The drawings are objected to for reasons as stated on FORM PTO-948 (Rev. 8-98). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Specification

3. The disclosure is objected to because of the following informalities: (1) " mm2" in line 20 of page 16 should be "mm^2 "; and (2) " 59mer " should be " 59 mer". Please check the specification for mistakes.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands, does not reasonably provide enablement for a method of immobilizing a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Note that claims 2-14 are dependent on claim 1.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 547. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary & The Amount of Direction or Guidance Provided

Claims 1 and 3-7 in this instant application are directed to a method of immobilizing a polynucleotide probe wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands.

The claims have sufficient breadth of scope so to encompass a method of immobilizing a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands. The specification (pages 12-18) provides limited guidance for a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands. The specification does not provide adequate guidance for a method of immobilizing a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands which the claims are directed to.

With the specification exemplifying a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands, and suggesting other steps, the skilled artisan is left to extrapolate a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands to a method of immobilizing a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands, and other is single-stranded having complementarity with one of the complementary strands.

Since the specification does not provide adequate guidance for a method of immobilizing a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands, it would take the skilled artisans several years to figure out the experimental conditions with little, if any, variable expectation of success. Such efforts constitute

undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In order to practice the full scope of the invention, the skilled artisan will have to resolve the following issues after immobilizing a polynucleotide probe wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands: (1) how to isolating the

immobilized probe; (2) how to amplifying the immobilized probe and then detecting resultant amplified probe; and (3) how to releasing and amplifying the probe. It would require several years for the skilled artisan to resolve each of these issues, assuming that such is achievable.

The Presence or Absence of Working Examples

The specification (pages 12-18) provides a working example for a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probes and the target wherein the probe is with hairpin structure or a double stranded PCR product and target is single-stranded nucleic acids immobilized on a microarray with a polycationic surfaces.

The Nature of the Invention

The invention relates to a method of immobilizing a polynucleotide probe wherein at least one of the probe and target is double-stranded comprising complementary strands, and other is single-stranded having complementarity with one of the complementary strands

The State of the Prior Art

At the time of filling, a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands has been known in the art (Bates *et al.*, Nucleic Acids Res. 23, 3627-3632, 1995). However, a method of immobilizing

a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands, and other is single-stranded having complementarity with one of the complementary strands is a novel and an undeveloped area of the art.

The Relative Skill of Those in the Art

The relative skill of those in the art to which the invention most closely pertains is high, on par with those which hold a Ph.D. in biochemistry and computer biology.

The Predictability or Unpredictability of the Art

Based on the limited guidance provided by the specification (pages 12-18), a skilled artisan can perform a method of immobilizing a polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of the probe and target is double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands. However, it is unpredictable whether a skilled artisan can perform a method of immobilizing a polynucleotide probe comprising the steps of : (1) isolating the immobilized probe; (2) amplifying the immobilized probe and then detecting resultant amplified probe; and (3) releasing and amplifying the probe wherein at least one of the probe and target is double-stranded comprising complementary strands, and other is single-stranded having complementarity with one of the complementary strands since the

specification does not provide guidances to show how to practice these method steps. Therefore, the predictability of the art is low. Further, the claimed invention relates directly to matters of physiology and chemistry which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The Breadth of the Claims

The claims encompass a method of immobilizing any kind of polynucleotide probe comprising the step of detecting specific hybridization of the probe and the target wherein at least one of any kind of probe and any kind of target is full or partial double-stranded comprising complementary strands and other is single-stranded having complementarity with one of the complementary strands.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 8, 11, 15, 16, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Bates *et al.*, (Nucleic Acids Res. 23, 3627-3632, 1995).

Bates *et al.*, teach detection and kinetic studies of triplex formation by oligodeoxynucleotides using real-time biomolecular interaction analysis (BIA). In this study, 5'-Biotinylated oligonucleotides were immobilized on the streptavidin-coated surface of a biosensor chip (page 3628, right column, first and second paragraphs) and subsequently hybridized to their complementary strand. Sequence-specific triplex formation was observed when a suitable third-strand oligopyrimidine was injected over the surface-bound duplex (page 3628, right column, last paragraph). In addition, a single-stranded oligonucleotide immobilized on the chip surface was able to capture a DNA duplex by triplex recognition. For example, Bt-T30 immobilized on the chip surface has been shown to capture of T30-A30 duplex (see second paragraph of left column in page 3629, fourth paragraph of left column in page 3630, Figure 4 and Figure 2 for sequences of oligonucleotides). This prior art meets the limitation of the claims.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 2, and 5-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.*, (Nature Biotechnology 14, 303-308, March 1996) in view of and Brown *et al.*, (US Patent 5, 807, 522 , filed on June 7, 1995) and Pease et al., (Proc. Natl. Acad. Sci. USA 91, 5022-5026, 1994), and in further in view of Ellouze *et al.*, (J. Biochem. 121, 521-526, 1997).

Tyagi *et al.*, teach fluoresce upon hybridization using molecular beacons as probes (see page 304, Figure 1). These probes undergo a spontaneous fluorogenic conformational change when they hybridize to their targets. Only perfectly complementary targets elicit this response, as hybridization does not occur when the target contains a mismatched nucleotide or a deletion. The probes are particularly suited for monitoring the synthesis of specific nucleic acids in real time. When used in nucleic acid amplification assays, gene detection is homogeneous and sensitive, and can be carried out in a sealed tube (page 303, abstract). Note that one of molecular beacon probes (molecular beacon A) used in this study consists of a 15-nucleotide-long-probe sequence embedded within two complementary 5-nucleotide-long arm sequences. The fluorophore, EDANS is joined to the 5'-terminal phosphate by a $-(CH_2)_6-S-CH_2-CO-$linker; and the quencher,

DABCYL, is joined to the 39-terminal hybroxyl group by a -$(CH_2)_7$-NH-linker. The probe comprises covalently linked complementary strands and is hairpin structure (page 304, Figure 2). This prior art encompasses some embodiments/limitations of claims 1, 2, 8-10, and 15-22.

Tyagi *et al.*, do not disclose: (1) microarray; (2) effect of metal ion on the enhancement of hybridization of the target and probe; and (3) the solid support with a polycationic surface.

Brown *et al.*, teach methods for fabricating microarrays of biological samples. The microarrays were fabricated on microscope slides which were coated with a layer of poly-l-lysine (Sigma) (column 16, lines 23 and 24). The amount of this polycationic polymer added was sufficient to form at least a monolayer of polymers on the glass surface. The polymer was bound to surface via electrostatic binding between negative silyl-OH groups on the surface and charged amine groups in the polymers. Poly-l-lysine coated glass slides might be obtained commercially, e.g., from Sigma Chemical Co. (St. Louis, Mo.) (Column 13, last paragraph). More generally, there is provided a substrate for use in detecting binding of labeled polynucleotides to one or more of a plurality different-sequence, immobilized polynucleotides. The substrate includes, in one aspect, a glass support, a coating of a polycationic polymer, such as polylysine, on said surface of the support, and an array of distinct polynucleotides electrostatically bound non-covalently to said coating, where each distinct biopolymer is disposed at a separate, defined position in a surface array of polynucleotides (column 4, fifth paragraph). In example 2, the cDNA clones were spotted on poly-l-lysine coated microscope slides. Total poly-A mRNA from wild type Arabidopsis was isolated using standard methods (Maniatis, et al., 1989) and reverse transcribed into total cDNA, using a fluorescein nucleotide analog to label the cDNA product (green

fluorescence). cDNA copies of mRNA from the transgenic plant were labeled with a lissamine nucleotide analog (red fluorescence). Two micrograms of the cDNA products from each type of plant were pooled together and hybridized to the cDNA clone array in a 10 microliter hybridization reaction (fifth and sixth paragraphs of column 17). Genes equally expressed in wild type and the transgenic Arabidopsis appeared yellow due to equal contributions of the green and red fluorescence to the final signal. The dots were different intensities of yellow indicating various levels of gene expression (second paragraph of column 18). This prior art encompasses some embodiments/limitations of claims 1, 2, 8, 10, 11, 14-16, 21, and 23.

Brown *et al.*, do not disclose: (1) PCR; (2) double-stranded probe with covalently linked complementary strands which linked through a first coupling moiety on one strand and a second coupling moiety on the second strand; (3) effect of metal ion on the enhancement of hybridization of the target and probe; and (4) single stranded target.

Pease *et al.*, teach light-generated oligonucleotide arrays for rapid DNA sequence analysis. They reported that modern photolithographic techniques could be used to facilitate sequence analysis by generating miniaturized arrays of densely packed oligonucleotide probes. These probe arrays, or DNA chips, could then be applied to parallel DNA hybridization analysis, directly yielding sequence information. In a preliminary experiment, a 1.28 x 1.28 cm array of 256 different octanucleotides was produced. The hybridization pattern of fluorescently labeled oligonucleotide targets was then detected by epifluorescence microscopy. This prior art encompasses some embodiments/limitations of claims 1, 2, 10, 11, 15, 16, and 21-23.

Pease *et al.*, do not teach (1) PCR; (2) double-stranded probe with covalently linked complementary strands which linked through a first coupling moiety on one strand and a second coupling moiety on the second strand; (3) effect of metal ion on the enhancement of hybridization of the target and probe; and (4) the solid support with a polycationic surface.

Ellouze *et al.*, teach the effect of divalent on formation and dissociation kinetics of T:A:T triple-stranded DNA. In this study, the formation and dissociation kinetics of homonucleotide oligo(dT):oligo(dA):oligo(dT) triplex were analyzed by fluorescence measurements of fluorescein-labeled oligo(dT) providing considerably higher sensitivity to monitoring reaction kinetics than traditional hypochromicity and circular dichroism. The triplex was formed by the addition of the oligo(dT) strand to a preserved oligo(dT):oligo(dA) duplex. The association rate was found to be faster the higher the divalent cation concentration and depends upon the nature of divalent ions in the following order of efficiency: $Mn^{2+} > Mg^{2+} > Ni^{2+}$, $Ca^{2+} > Ba^{2+}$. The more efficient metal ions for the triplex formation were found also more efficient for the stabilization. The dissociation kinetics of the third Hoogsteen-bound strand was monitored at below melting temperature by chasing the labeled dT strand from the triplex by excess of non-labeled oligonucleotide. The dissociation rate was found to be almost independent of concentration and nature of cation. They suggested that the thermodynamic stabilization of triplex by cations was a consequence of the increased formation rate (page 521, abstract). This prior art encompasses some embodiments/limitations of claims 1, 12, and 13.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have immobilized single stranded targets on a microarray comprised a polycationic

surface as suggested by Pease *et al.*, and Brown *et al.*, and hybridized single stranded targets in the presence of a divalent cation as suggested by Ellouze *et al.*, using a probe with a structure of molecular beacons containing partial double strand region wherein complementary strands are both covalently and noncovalently linked as suggested by Tyagi *et al.*. The method provided by Brown *et al.*, would have motivated one having ordinary skill in the art to immobilize single stranded targets on a microarray comprised a polycationic surface because Pease *et al.*, have been shown the arrays or chips with single stranded target could be made and applied to parallel DNA hybridization analysis. The methods provided by Ellouze *et al.*, and Tyagi *et al.*, would have motivated one having ordinary skill in the art to hybridize single stranded targets immobilized on a microarray in the presence of a divalent cation using a probe containing partial double strand region wherein complementary strands are both covalently and noncovalently linked because divalent cations have been shown to enhance hybridization of nucleic acid triplex formation and a probe with a structure of molecular beacons containing partial double strand region could be used for hybridization. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to combine these methods together because all of these methods are known in the art and are easy to use.

Conclusion

9. No claim is allowed.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
September 6, 2000

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600